RESEARCH REPORT

A prospective study of delayed sleep phase syndrome in patients with severe resistant obsessive-compulsive disorder

JO TURNER, LYNNE M. DRUMMOND, SUMAN MUKHOPADHYAY, HAMID GHODSE, SARAH WHITE, ANUSHA PILLAY, NAOMI A. FINEBERG

Behavioural Cognitive Psychotherapy Unit, Springfield Hospital, London SW17 7DJ, UK

There have been relatively few studies examining sleep in patients with obsessive-compulsive disorder (OCD) and these have produced contradictory findings. A recent retrospective study identified a possible association between OCD and a circadian rhythm sleep disorder known as delayed sleep phase syndrome (DSPS). Patients with this pattern of sleeping go to bed and get up much later than normal. They are unable to shift their sleep to an earlier time and, as a result, suffer considerable disruption to social and occupational functioning. In this study, we examined the sleep of patients with OCD prospectively. We aimed to establish the frequency of DSPS in this population and any associated clinical or demographic factors which might be implicated in its aetiology.

Key words: Obsessive-compulsive disorder, delayed sleep phase syndrome, circadian rhythms

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Obsessive-compulsive disorder (OCD) is a common, chronic disorder which results in marked distress and impairment of social and occupational functioning. Sleep disturbance often accompanies mental disorders, but there have been few studies of sleep disturbance in OCD. These have produced contradictory findings, with some reporting sleep disruption, and others a normal sleep pattern (1-3).

In a study by Bobdey et al (4), the sleep patterns of non-depressed OCD patients did not differ significantly from controls. There was, however, a small subgroup of patients who went to bed and arose much later than normal. This delayed pattern of sleeping, known as delayed sleep phase syndrome (DSPS), results in daytime sleepiness and major disruption of work and social functioning (5). It is the commonest form of circadian rhythm sleep disorders (6), which are defined as a mismatch between the usual daily schedule required by the individual's environment and his or her endogenous circadian sleep-wake system (7,8).

In a recent retrospective study, we identified a possible association between OCD and DSPS (9). The present study aims to examine sleep patterns in OCD prospectively, to establish the frequency of DSPS in this population, and to explore its clinical impact and any associated factors which might be implicated in its aetiology.

METHODS

The study was granted clinical approval by Wandsworth ethics committee, and all subjects gave informed consent. Consecutive admissions with a DSM-IV diagnosis of OCD to the inpatient unit of the Behavioural Cognitive Psychotherapy Unit at Springfield Hospital, London from August 1, 2003 to July 31, 2005 were invited to enter the study. This unit offers specialist treatment for patients with severe resistant OCD using predominantly psychological methods (10). To be accepted by the unit, patients must have already failed at least one trial of outpatient cognitive behavioural therapy (CBT) plus two trials of a serotonin reuptake inhibitor (clomipramine or a selective serotonin reuptake inhibitor, SSRI).

Within a week of admission, prior to commencing any treatment, subjects were assessed using a range of validated instruments. Symptoms and severity of the OCD were measured using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) checklist and severity scale (11), the Padua Inventory (12) and the Compulsion Activity Checklist (CAC) (13). Comorbid depression was assessed using the Montgomery-Asberg Depression Scale (MADRS) (14) and the Beck Depression Inventory (BDI) (15). The Sheehan Disability Scale (16), a self-rated instrument measuring impairment in work, family and social functioning during the past month, was used to assess the degree of disability. All subjects provided both retrospective and prospective data on their sleep using the sleep measures outlined below. In addition, the patients' sleep patterns were observed and recorded by nursing staff over five consecutive nights. Demographic data, alcohol and medication use were also recorded.

Patients with comorbid DSM-IV major depressive disorder, schizophrenia or serious physical illness were excluded, as these are known to interfere with sleep.

The sleep measures included the Pittsburgh Sleep Quality Inventory (PSQI, 17), the St. George's Hospital Medical School Insomnia Questionnaire (18), and objective assessment of sleep. The PSQI is a retrospective self-report questionnaire covering the previous month's sleep. It comprises nineteen self-rated items, which combine to seven component scores, measuring subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleeping medication and daytime dysfunction. The St.

George's Hospital Medical School Insomnia Questionnaire is a self-report questionnaire on the previous night's sleep, which patients were asked to complete over five consecutive nights, after a two-night "settling in" period. For the objective assessment of sleep, settling and rising times plus time asleep were recorded by nursing staff who checked the patients hourly over the same five-night period.

We used DSM-IV criteria for circadian rhythm sleep disorder, delayed sleep phase type (307.45), except item C, which excludes concurrent mental illness. In addition, we operationally defined DSPS as regularly falling asleep later than 1.00 am and awakening after 10.00 am. The choice of timing was based on previous research (19). Non-phase shift (NPS) was defined as falling asleep before midnight and awakening before 9.00 am. Subjects were categorised as DSPS or NPS on the basis of their sleep pattern over the five-night observation period and the history of usual sleep pattern obtained from the PSQI. Some patients who did not persistently display either DSPS or NPS patterns were excluded from the analysis.

Patients with DSPS were compared to their non-phase shifted counterparts on measures of illness severity, symptom profile and standardized parameters of sleep. Age, sex, ethnicity, duration of illness, concomitant medication, hypnotic use and alcohol or substance misuse were also compared. The Y-BOCS symptom checklist was used to establish if rituals occurred around bedtime. Patients with DSPS were asked to evaluate if their bedtime was delayed because of rituals, if they were happy with their sleep pattern and whether this pattern pre- or post-dated the OCD.

The two groups were compared with respect to age variables and standardized measures using unpaired t-tests, as despite the relatively small sample size the data did indicate a normal distribution. They were compared with respect to categorical variables using chi-squared tests.

RESULTS

Thirty-one out of 36 consecutive admissions consented to participate in the study. Of these, 13 fulfilled criteria for DSPS, 15 had a normal sleep phase and three fell into neither category and thus were not included in the analysis (Table 1). Compared to the NPS group, patients with DSPS were significantly more likely to be male, were significantly younger and had more severe OCD based on significantly higher scores on the Y-BOCS, Padua Inventory and CAC. DSPS patients were also more disabled than patients with a normal sleep phase based on significantly higher scores on the Sheehan's Disability Scale. Levels of depression based on scores on the MADRS and BDI were not significantly different between the two groups.

With regard to previous treatment, all patients had received at least one trial of outpatient CBT. All but one patient, who was in the DSPS group, had received two trials of clomipramine or an SSRI. This individual refused all medication based on obsessional fears. Augmentation with an antipsychotic had been given to seven patients with normal sleep phase and four with DSPS. Three patients in the NPS group had received augmentation with a mood stabilizer, two with sodium valproate and one with carbamazepine. One patient in the DSPS group had been given lithium augmentation. All four patients remained on mood stabilizers throughout the study. No patient had previously had psychosurgery.

Table 1 Characteristics of OCD patients with phase-shifted sleep compared to those with a normal sleep phase

	Phase-shifted (N=13)	Non-shifted (N=15)
Sex (% males)	76.9*	40.0
Ethnicity (% Caucasian)	92.3	86.7
Age (years, mean ± SD)	29.3 ± 12.2**	41.4 ± 13.4
Age at onset (years, mean ± SD)	16.4 ± 9.2	22.4 ± 10.8
Score on CAC (mean ± SD)	48.5 ± 19.4***	26.1 ± 16.7
Score on Padua Inventory (mean ± SD)	108.7 ± 30.8***	55.1 ± 25.4
Total score on Y-BOCS (mean ± SD)	32.4 ± 3.5***	24.3 ± 3.7
Score on BDI (mean ± SD)	25.4 ± 13.2	18.4 ± 10.7
Score on MADRS (mean ± SD)	14.2 ± 2.1	12.9 ± 2.7
Global score on PSQI (mean ± SD)	7.8 ± 2.6	6.0 ± 2.8
Global score on Sheehan Disability Scale (mean ± SD)	22.2 ± 2.0***	17.9 ± 4.0

*p<0.05; **p<0.02; ***p<0.01

OCD - obsessive-compulsive disorder; CAC - Compulsion Activity Checklist; Y-BOCS - Yale-Brown Obsessive Compulsive Scale; BDI - Beck Depression Inventory; MADRS - Montgomery-Asberg Depression Scale; PSQI - Pittsburgh Sleep Quality Inventory

At the time of the study, the majority of patients in both groups were taking an antidepressant, most commonly an SSRI. Prescribed hypnotics (temazepam 10 mg or zopiclone 3.5 mg) were being taken by two patients in the DSPS group. One patient was taking zopiclone 7.5 mg in the NPS group. Four patients in each group were also taking an antipsychotic (olanzapine, risperidone, sulpiride or quetiapine). Two patients with DSPS and one with normal sleep phase were on no medication. There was no difference in reported alcohol use between the two groups and no illicit drug use was reported.

Subjective sleep quality, based on scores on the PSQI, was worse for patients with phase-shifted sleep, but this failed to reach significance. There was also no significant difference between the two groups for subjective sleep latency, sleep duration, sleep efficiency, sleep disturbance and daytime dysfunction. Mean objective sleep latency, i.e., time taken to fall asleep as measured by nursing staff, was 33 minutes for patients with phase-shift compared to 43 minutes for their non-phase shifted counterparts. Again, this difference was not significant.

All but one patient from each group had rituals which occurred around bedtime. Of the patients with DSPS, none believed rituals to be the cause of their delayed sleep pattern. They also reported that they were unhappy with this pattern and that the onset of the shifted sleep phase was after the onset of OCD.

Of the three patients who had neither a normal or delayed sleep phase, two went to bed at a normal time (i.e., around 11.00 pm) but slept for a prolonged period (average 12 hours) and the third had no discernable pattern. Both patients with prolonged sleep described having a normal length but delayed sleep phase pattern in the past.

DISCUSSION

In this study, 42% of patients with severe resistant OCD had DSPS. Patients with DSPS were significantly more likely to be male, were younger and had more severe OCD than those with a normal sleep phase. Apart from the timing of sleep, there was no significant difference on any other parameter of sleep as measured by the PSQI or the objective nursing assessment. This concurs with Weitzman's (5) finding that sleep is essentially normal in DSPS, albeit at a later time. The delayed sleep phase was not due to patients taking longer to fall asleep, as there was no significant difference in sleep latency as measured by nursing staff. Those with DSPS were also no more likely to have bedtime rituals, and patients themselves denied this as the reason for going to bed late. Use of hypnotics and other medications was also similar between the two groups. All the patients with a phase-shifted sleep pattern expressed dissatisfaction with the timing of their sleep and were unable to explain why the shift had occurred. Patients with DSPS were significantly more disabled in their social and occupational functioning than those with a normal sleep. It is uncertain whether this is due to the shifted sleep pattern itself or reflects the fact that this group had more severe OCD.

DSPS is uncommon in the general adult population: estimates of 0.17-0.72% have been reported (20). However, a prevalence of 7.3% has been found among adolescents (7) and up to 10% of otherwise normal children (21). Onset of DSPS is usually in childhood or adolescence. No difference between the sexes has been found and a familial trait has been noted in 44% of patients (6).

There are relatively few studies examining DSPS in patients with mental disorders. An association between OCD and DSPS has not previously been reported. However, patients with OCD are notoriously secretive about their problems, which they often conceal for many years. An OCD diagnosis may thus often be missed. This study suggests that DSPS is a common problem in patients with chronic severe OCD. A retrospective study of similar OCD patients found a prevalence rate of 17% with DSPS (18).

In Weitzman's series (5) of 30 patients presenting to an insomnia clinic with DSPS, 17 were found to have no mental disorder; two had chronic schizophrenia; one manic-depressive disorder; four chronic depression and six personality disorder. In a study of 33 patients with DSPS referred to a sleep disorders clinic, Regestein and Monk (19) reported that 75% were, or had been, depressed. This assertion, however, was only based on current or previous antidepressant use. In 14 of 22 adolescents with DSPS, Thorpy et al (22) found symptoms of depression and suggested a primary psychiatric cause for the sleep disturbance. Weitzman (5) turns this suggestion around and claims psychological symptoms are not the cause, but a product of the problem, quoting the evidence that many DSPS patients show a dramatic improvement in psychological functioning after treatment of the sleep disorder. Other authors support the suggestion that DSPS precedes and may contribute to the development of mental disorder. Dagan et al (23,24) found a high incidence of personality disorder in patients with DSPS and suggested that a mismatch between the individual's biological clock and the environment leads to emotional and social problems. Patients in our study, however, reported that sleep phase shift developed after the onset of OCD.

From early childhood, the cycle of wakefulness and sleepiness is regulated by a circadian "clock" in the suprachiasmatic nucleus of the hypothalamus. A typical adult's endogenous sleep-wake cycle is slightly more than 24 hours and hence must be reset daily to keep it aligned with the external 24-hour day. The circadian clock is regulated by various cues, such as the light-dark cycle of day and night. Bright light presented early during the wake period tends to produce a phase advance of sleep but, if presented late, produces a phase delay. Social cues such as mealtimes and activity also play a role in the regulation of the sleep-wake cycle, either acting in conflict or helping to stabilize phase relationships. Interference with normal regulation can occur as a result of consumption of caffeine, alcohol or drugs.

The effect of light on the sleep-wake cycle is mediated via melatonin. The secretion of melatonin is stimulated by the dimming of light in the evening and is suppressed by bright light during the day. The evening rise in melatonin precedes the onset of sleepiness by approximately 1.5-2 hours (25). Serotonin is involved in the resetting process both indirectly via melatonin and through direct action on the suprachiasmatic nucleus. It follows that any medication acting on the serotonergic system could influence the sleep-wake cycle. In a study by Hermesh et al (26), 10 patients with OCD developed DSPS after starting fluvoxamine. All patients were taking only fluvoxamine and, in 9 out of 10, DSPS disappeared on withdrawal of the drug. The authors also noted that 7 out of 10 patients had taken fluoxetine and/or clomipramine in the past and had not developed this sleep disturbance. The authors concluded that the DSPS was attributable to fluvoxamine rather than OCD itself. A possible mechanism for the differential effect of fluvoxamine and fluoxetine is the different impact these drugs have on melatonin levels (26, 27). In our study, of the patients with DSPS, none was on fluvoxamine and just one was taking fluoxetine.

It has been suggested that people who develop DSPS do so because they are unable to adequately reset their biological clocks (5). One explanation for difficulty in producing the necessary phase advance of sleep is that indi-

viduals with DSPS have an unusually long endogenous circadian period. In studies of the spontaneous circadian rhythms of young adults living in temporal isolation, most developed sleep-wake cycles of around 25 hours, but in some subjects the cycle extended to up to 50 hours (19). Differences between individuals are partly accounted for by genotype. Several genes are involved in the regulation of human circadian rhythms, and familial forms of DSPS are associated with mutations in one or other of the clock genes. Age is also a factor: the endogenous cycle is longer in early life and tends to shorten in middle and old age. This may account for the overrepresentation of DSPS in adolescents and young adults (19) and for our finding of significantly younger age in patients with DSPS.

With an understanding of how the sleep-wake cycle is regulated, we can hypothesize about the mechanisms by which DSPS might develop in our patients with severe OCD. Lengthy or complex rituals can render patients housebound, resulting in inadequate exposure to morning light that in turn produces a phase delay of sleep. Social isolation, lack of activity and difficulty preparing regular meals, also common in severe OCD, would compound the problem by impeding the daily resetting of the biological clock. There is also some evidence for abnormalities in the circadian secretion of melatonin in patients with OCD. In a study of circadian rhythms in 13 medication-free OCD patients, Monteleone et al (28) found the night-time peak of melatonin levels was significantly lower than in controls and occurred 2 hours later. This difference was more pronounced in patients with more severe OCD based on higher Y-BOCS scores. A later peak melatonin time would typically produce a phase delay of sleep.

The importance of light and melatonin in the regulation of the sleep-wake cycle suggests a possible role for treatment with exogenous melatonin and/or light therapy in OCD patients with this disabling sleep disturbance. Further research examining biological processes in DSPS and OCD are warranted, which may lead to future pharmacological treatments for both conditions.

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